Adenovirus Vaccine Restoration A Clinical Perspective

Presentation to Armed Forces Epidemiological Board

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Outline

- Vaccine Development 2005
- Adenovirus Vaccine Phase 1 Trial
- Wyeth Vaccine Experience
- Future Clinical Development: Points to Consider

Stages of Review and Regulation

Clinical Investigational Plan

IND

Phase 1
Safety
Immuno-genicity

Phase 2
Immuno-genicity
Safety
Dose Ranging

Phase 3
Efficacy
Safety
Immuno-genicity

BLA
Data to support approval; Inspection

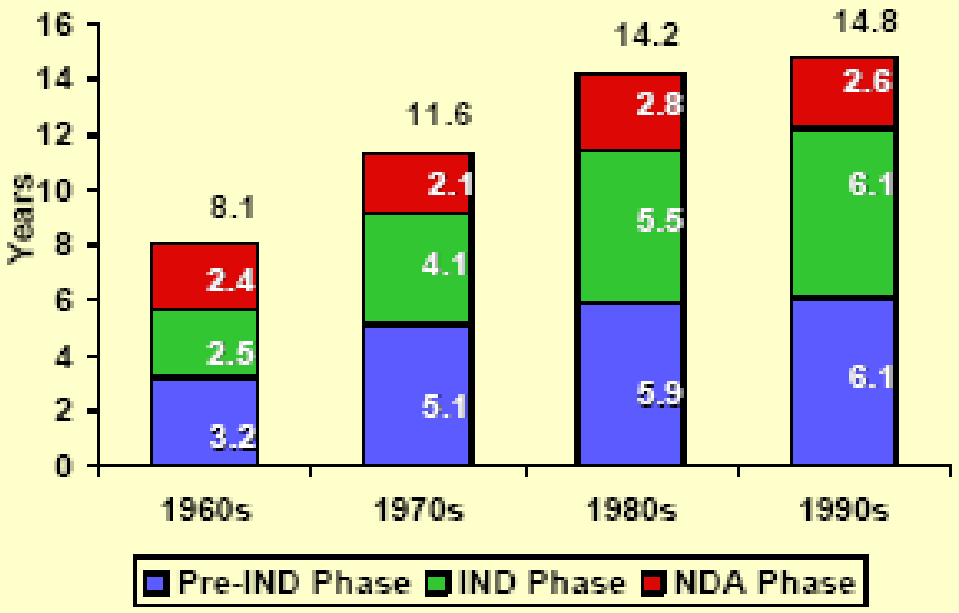
Phase 4
Inspection
Safety
Efficacy
Lot Release

BLA Supplement
(BLA Suppl)
Post-approval Changes:
New Indications
Dosing
Manufacture
Equip./Facilities

Establishment of Manufacturing and Testing Controls, Specifications

IND =Investigational New Drug Application;
BLA=Biologics License Application

R&D Cycle Times are Increasing



Source: Joseph A. DiMasi, "New Drug Development Cost, Risk, and Complexity," Drug Information Journal, May 1995. (From R&D Directions, 1995)

Development times for vaccines are the same or longer

From Dr. Jill G Hackell
AVP Scientific Affairs and Res Strategy

Clinical Development Status

A Phase 1, Randomized, Double-Blind, Placebo Controlled Study to Evaluate The Safety And Immunogenicity Of The Live, Oral Type-4 and Type-7 Adenovirus Vaccines

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Brooke Army Medical Center PI: Dr. Jenice Longfield
AMEDD Center and School
Walter Reed Army Medical Center
Naval Health Research Center
U.S. Army Medical Materiel Development Activity
Duramed Research, Inc (Barr Laboratories)

Phase 1 Study Objectives

Primary:

1. Evaluation of the safety of the Barr type 4 and type 7 oral adenovirus vaccines administered together.

Secondary:

1. Serotype 4 and 7 neutralizing antibody seroconversion and titer

2. Duration of vaccine virus shedding in the stool and throat secretions in vaccine recipients.

Rationale

- Military subjects to simulate BT
- Minimize potential secondary spread of vaccine virus
- Low likelihood of active Adv 4 or 7 circulation*
- Relative ease in recruitment

Pre-Phase 1 Seroprevalence Study

Objective:

Serotype 4 and type 7 seroprevalence among 91W's

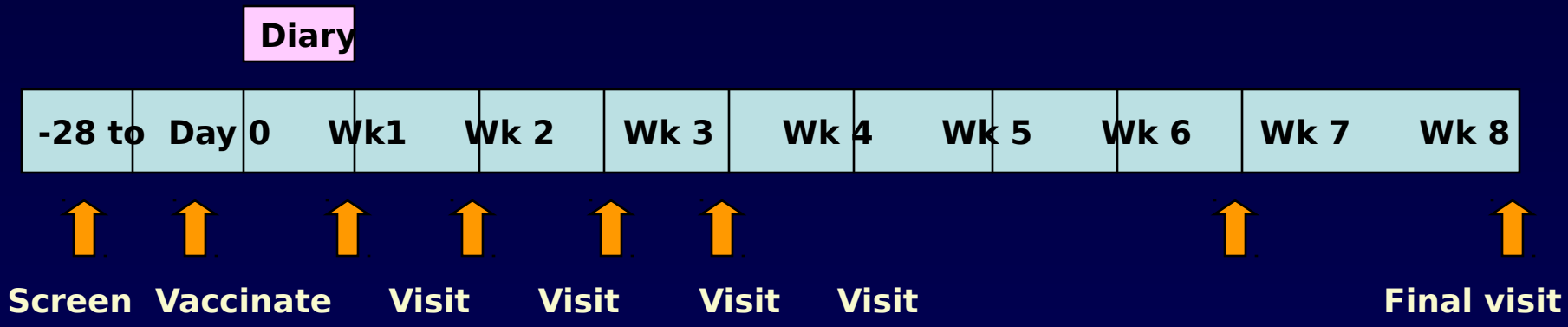
Results:

99 91W blood donors tested

Adv 4 (+)	Adv 7 (+)	69%	
Adv 4 (-)	Adv 7 (+)		9%
Adv 4 (+)	Adv 7 (-)	20%	
Adv 4 (-)	Adv 7 (-)		2%

Adv 4 seropositive	89%
Adv 7 seroposivive	78%

Study Design



Serology: Screen, Day 0, Wks 1,2,4,8
Throat: Day 0, Wks 1,2,3,4,8
Stool or rectal swab: Day 0, Wks 1,2,3,4,8
Viremia: Day 0, Wks 1,2,4,8
All febrile ARD worked up

Inclusion/Exclusion

- Healthy 18-40 yo
- Informed Consent
- If female, not pregnant or nursing
- Seronegative to at least one serotype (4 or 7)
- No prior enlisted military service before 1998
- No hx of major medical illnesses
- No acute illness or abnormal physical exam
- No HIV, active Hep B, C
- No other vaccinations within 30 days prior to Day 0

Subject population

407 91W antibody screened

Adv 4 (+)	**Adv 7 (+)**	**68%**	
Adv 4 (-)	**Adv 7 (+)**	**14%**	
Adv 4 (+)	**Adv 7 (-)**		**14%**
Adv 4 (-)	**Adv 7 (-)**		**4%**
Adv 4 seropositive			**82%**
Adv 7 seroposivive		**82%**	

Adenovirus 4 and 7 Seroprevalence

	No. Subjects	Adv 4(+)	Adv 7(+)
Pre-induction* 1998	303	34%	27%
Post-BT** 1964	120	25%	-
Post-BT 2004	407	82%	82%

*Ludwig, et al JID 1998;178:1776-8

**Forsyth, et al Am J Hyg 1964;80:343-55

Subject population

- 58 seronegative volunteers enrolled (14%)

Adv 4 (+)	**Adv 7 (+)**	**0%**	**22%**	
Adv 4 (-)	**Adv 7 (+)**		**47%**	**24%**
Adv 4 (+)	**Adv 7 (-)**	**43%**	**41%**	
Adv 4 (-)	**Adv 7 (-)**	**10%**	**12%**	
Adv 4 seropositive		**43%**	**63%**	
Adv 7 seroposivive		**47%**	**46%**	

- 30 vaccinated, 28 received placebo
- 54 volunteers completed study
  - 4 dropped out (not vaccine related)

Results: Safety

Adverse Events	Vaccine* (N=30)	Placebo (N=28)
Nasal Congestion	10 (33.3%)	16 (57.1%)
Cough	10 (33.3%)	10 (35.7%)
Sore throat	8 (26.7%)	8 (28.6%)
Headache	6 (20.0%)	6 (21.4%)
Fever	2 (6.7%)	6 (21.4%)
Arthralgia	4 (13.3%)	0 (0.0%)
Nausea	4 (13.3%)	6 (21.4%)
Rhinorrhea	1 (3.3%)	3 (10.7%)
Wheezing	1 (3.3%)	3 (10.7%)
Pneumonia	1 (3.3%)	3 (10.7%)
Sinusitis	3 (10.0%)	2 (7.1%)
Abdominal pain	5 (16.7%)	1 (3.6%)
Diarrhea	4 (13.3%)	2 (7.1%)

* None differ significantly from placebo

SAE's

Day 0-56 Hospitalizations

- 2 pneumonias (one vaccine, one placebo)
- 1 ARD (placebo)

Day 180 Hospitalizations

- "appendicitis" (vaccine)
- MRSA thigh abscess (placebo)

Results: Virus Shedding

Table 9.1. Adenovirus Isolation from Fecal Specimen by Treatment Group and Pre-immunization Antibody Status Over Time – All Treated Subjects

	VACCINE			PLACEBO		
Type 4	**Antibody (-)**	**Antibody (+)**	**Total**	**Antibody (-)**	**Antibody (+)**	**Total**
Stool Virus	**(+) / N**	**(+) / N**	**(+) / N**	**(+) / N**	**(+) / N**	**(+) / N**
Day 0	0 / 11	0 / 19	0 / 30	0 / 10	0 / 18	0 / 28
Day 7	7 / 11	0 / 18	7 / 29	1 / 10	0 / 17	1 / 27
Day 14	6 / 11	0 / 18	6 / 29	1 / 9	0 / 17	1 / 26
Day 21	1 / 11	0 / 18	1 / 29	0 / 9	0 / 17	0 / 26
Day 28	0 / 11	0 / 18	0 / 29	0 / 9	0 / 16	0 / 25
Day 56	0 / 11	0 / 18	0 / 29	0 / 9	0 / 16	0 / 25
Overall*	8 / 11	0 / 19	8 / 30	2 / 10	0 / 18	2 / 28
Type 7	**Antibody (-)**	**Antibody (+)**	**Total**	**Antibody (-)**	**Antibody (+)**	**Total**
Stool Virus	**(+) / N**	**(+) / N**	**(+) / N**	**(+) / N**	**(+) / N**	**(+) / N**
Day 0	0 / 17	0 / 13	0 / 30	0 / 14	0 / 14	0 / 28
Day 7	10 / 16	6 / 13	16 / 29	0 / 14	0 / 13	0 / 27
Day 14	5 / 16	3 / 13	8 / 29	0 / 13	0 / 13	0 / 26
Day 21	0 / 16	0 / 13	0 / 29	0 / 13	0 / 13	0 / 26
Day 28	0 / 16	0 / 13	0 / 29	0 / 13	0 / 12	0 / 25
Day 56	0 / 16	0 / 13	0 / 29	0 / 13	0 / 12	0 / 25
Overall*	12 / 17	6 / 13	18 / 30	0 / 14	0 / 14	0 / 28

*Subject who tested positive at multiple time points were only counted once for overall.

Subject population

30 Vaccinated

Adv 4 (+)	Adv 7 (+)	6 (20%)
Adv 4 (-)	Adv 7 (+)	7 (23%)
Adv 4 (+)	Adv 7 (-)	13 (43%)
Adv 4 (-)	Adv 7 (-)	4 (13%)

28 Placebo

Adv 4 (+)	Adv 7 (+)	7 (25%)
Adv 4 (-)	Adv 7 (+)	7 (25%)
Adv 4 (+)	Adv 7 (-)	11 (39%)
Adv 4 (-)	Adv 7 (-)	3 (11%)

Results: Immunogenicity

Table 7.2. Cumulative Seroconversion by Treatment Group Over Time

ADV Type 4 Cumulative Seroconversion				
	VACCINE (N*=11)		PLACEBO (N*=10)	
	Converted	%	Converted	%
Day 7	0	0	0	0.0
Day 14	6	54.5	2	20.0
Day 28	8	72.7	3	30.0
Day 56	9	81.8	3	30.0
ADV Type 7 Cumulative Seroconversion				
	VACCINE (N*=17)		PLACEBO (N*=14)	
	Converted	%	Converted	%
Day 7	0	0	0	0.0
Day 14	10	58.8	0	0.0
Day 28	11	64.7	0	0.0
Day 56	12	70.6	0	0.0

* N is the total number of subjects who were type 4 or type 7 sero-negative at Day 0

72.7% [39-94] 64.7% [38-86]

Phase 1 Study Summary

- Adenovirus 4 and 7 vaccines are safe; no training day lost
- Vaccine viral shedding limited to 21-28 days
- Evidence of wild-type Adv 4 circulation during study
- Immunogenicity estimated at 40-90%

WRAIR Wyeth Vaccine Study 1998

Objective: Characterize antibody response and viral she
from the licensed Wyeth Adv 4 and 7 vaccines

Subject population: 36 healthy 18-40 yo seronegative

Inclusion/Exclusion: Same

Schedule: 0, 3,7,10,14,21 and 28 days

Specimens: Serum, urine, throat and stool

Kuschner et al, unpublished data

Subject population

65 civilian/military subjects screened

Adv 4 seropositive 38% Adv 7 seroposivive 51%

Results: Safety

Adverse Events	Vaccine* (N=30)	Placebo (N=28)	Wyeth (N=36)
Nasal Congestion	10 (33.3%)	16 (57.1%)	4 (11.1%)
Cough	10 (33.3%)	10 (35.7%)	8 (22.2%)
Sore throat	8 (26.7%)	8 (28.6%)	10 (27.6%)
Headache	6 (20.0%)	6 (21.4%)	-
Fever	2 (6.7%)	6 (21.4%)	6 (21.4%)
Arthralgia	4 (13.3%)	0 (0.0%)	-
Nausea	4 (13.3%)	6 (21.4%)	-
Rhinorrhea	1 (3.3%)	3 (10.7%)	-
Wheezing	1 (3.3%)	3 (10.7%)	-
Pneumonia	1 (3.3%)	3 (10.7%)	-
Sinusitis	3 (10.0%)	2 (7.1%)	-
Abdominal pain	5 (16.7%)	1 (3.6%)	-
Diarrhea	4 (13.3%)	2 (7.1%)	13 (36.1%)

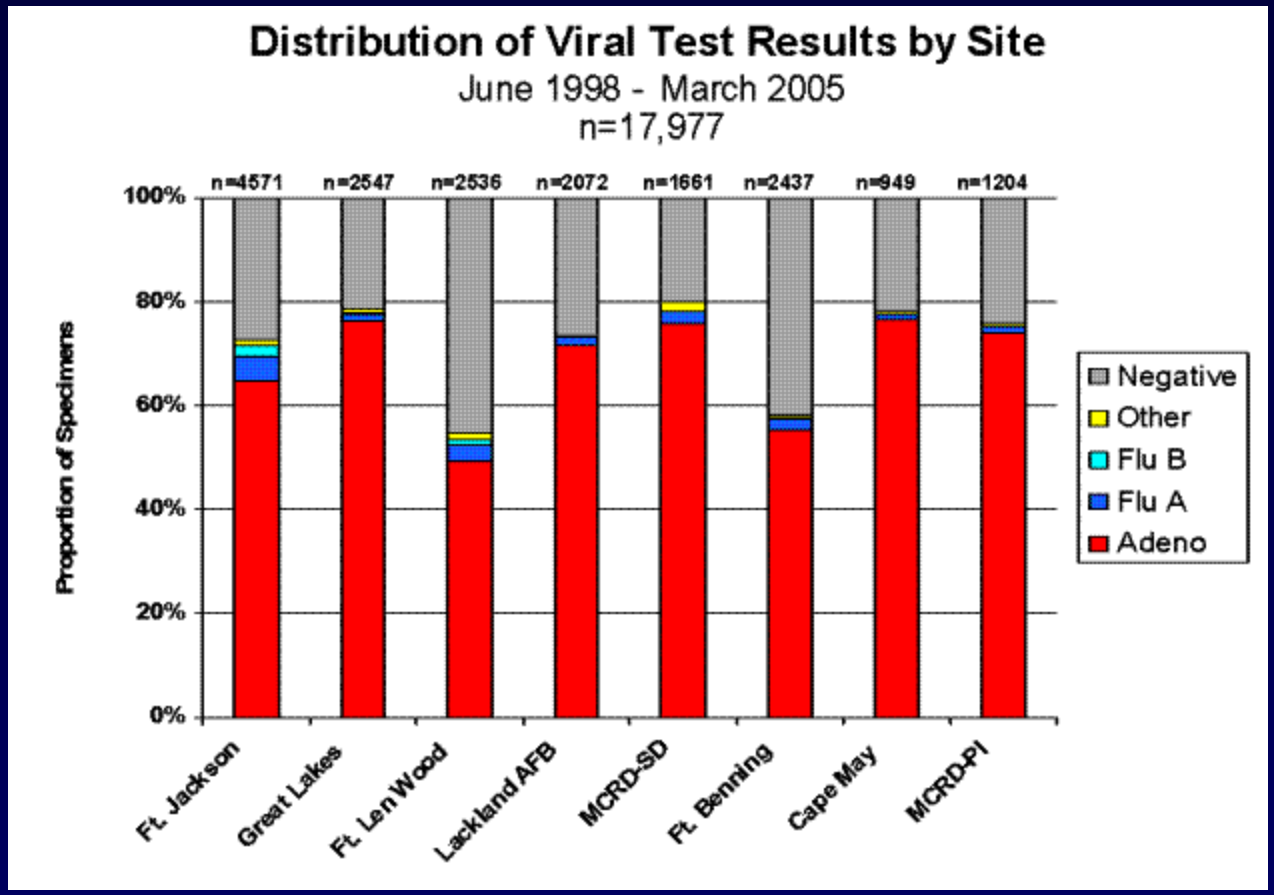
* None differ significantly from placebo

Results: Day 28 Immunogenicity

		Barr	Wyeth
Adv 4	Seroconv	8/11 (72.7%)* [39,94]	22/30 (73.3%) [54,88]
	GMT	13.9	10.7
Adv 7	Seroconv	11/17 (64.7%) [38,86]	12/13 (92.3%) [64,99]
	GMT	14.7	37.1

* 30% in placebo group

Current Adenovirus Epidemiology



Data from NHRC

Clinical Development Plan Points to Consider

- Next clinical trial being planned: Safety, Dose Immunogenicity, Manufacture consistency
- Efficacy and Correlate of Protection as Endpoints
- Access to military subject population
- What efficacy is licensable?
- What efficacy is required by DoD?
- “Post-marketing” surveillance
- Regulatory (FDA) guidance

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